The present invention discloses a strategy in which introduction of antigen presenting cells (APCs) expressing high levels of Fas ligand together with a specific antigen could induce specific, systemic tolerance to the antigen. A series of experiments were performed to examine tolerance induction *in vivo* by Fas ligand-expressing antigen presenting cells (Examples 17, 18, 20, 21 and Figures 7, 8, 10B and 11). It is shown that antigen presenting cells, which express Fas ligand and processed adenovirus antigens, can directly induce apoptosis of Fas-positive T cells resulting in adenovirus-specific T-cell tolerance. Pretreatment of recipient mice with the adenovirus-transfected antigen presenting cells that produce Fas ligand resulted in induction of T cell tolerance to the adenovirus. Induction of T cell tolerance to adenovirus required production of Fas ligand by the antigen presenting cells and did not occur with adenovirus-transfected, control antigen presenting cells. T cell tolerance also required production of Fas by the T cells of recipient mice, as Fas-deficient lpr/lpr mice could not be tolerized. The T cell tolerance was antigen-specific as there was normal T-cell response to murine cytomegalovirus (MCMV) in tolerized mice.

Applicants hereby submit a Declaration showing tolerance induction by Fas ligand-expressing antigen presenting cells disclosed

herein can be extended to other models of chronic inflammation and autoimmunity. The results in the Declaration demonstrate that Fas ligand-expressing antigen presenting cells can be used to down-modulate inflammatory response and autoimmunity resulted from viral- or pathogen-induced inflammatory responses.

In the Final Office Action mailed 3/23/2001, the Examiner contended that "there is no evidence of record to show that one skilled in the art would associate the said *in vivo* mouse method with successful method of inducing systemic immune tolerance in human." Applicants respectfully disagree.

Initially, Applicants submit that there is no evidence of record to show that one skilled in the art would NOT associate the said *in vivo* mouse method with successful method of inducing systemic immune tolerance in human. The Examiner has not pointed to any reference or combination of references to support her argument that a person having ordinary skill in this art would not reasonably expect Applicants' claimed method to induce systemic immune tolerance in humans. Instead, it appears the Examiner has put forth her own opinion.

Wrong
See Paper 20
mailed 3/23/01
@ § 10-11

Applicants submit that the specification of the application and the Declaration of Dr. Mountz has provided ample data showing

tolerance induction by Fas ligand-expressing antigen presenting cells in not one but multiple disease animal models well-recognized in the art. In view of the generalized application of the present invention in multiple disease models, Applicants submit that one of ordinary skill in the art would has sufficient reason and support to associate the claimed method with successful method of inducing systemic immune tolerance in human.

In the Final Office Action mailed 3/23/2001, the Examiner made reference to the death of a patient in a gene therapy trial. The patient "died following an acute respiratory system collapse and subsequent multi-organ failure, apparently brought on by a massive immune system response". Applicants submit that Applicants' claimed methodology is different and distinct from the above-referenced gene therapy trial and cause of death. The Examiner has not provided any scientific evidence that the results obtained in that specific University of Pennsylvania gene therapy trial would lead a person having ordinary skill in this art to reasonably expect Applicants' claimed methodology to fail.

Point- mouse wasn't predictive.

Applicants' claimed methodology is designed, at least in part, to down-regulate immune responses by the expression and function of Fas ligand. It is unlikely that Applicants' claimed

methodology would cause immune system over-reaction and death in a patient as described above. Therefore, the Examiner's citation of the of death that specific University of Pennsylvania gene therapy trial can not be used to invalidate the applicability of Applicants' claimed methodology in humans.

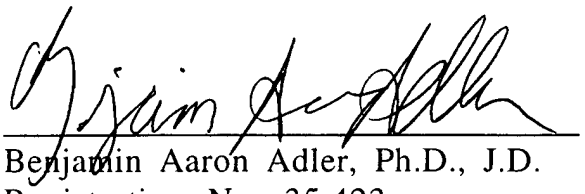
Furthermore, it is well established that neither clinical success nor clinical trials in humans is a prerequisite to patentability under U.S. patent law. The Applicants' specification supplies more than just in vitro data supporting the claimed methodology. In both the Applicants' specification and in the Declaration submitted herein, Applicants have provided sound animal model data supporting the claimed methodology. The Examiner has not provided any scientific evidence to the contrary.

Based on the arguments *supra*, Applicants submit that the detailed description of the effects of the Fas ligand-expressing antigen presenting cells *in vivo* disclosed in the specification has provided sufficient enablement for using said antigen presenting cells to induce tolerance *in vivo*. Accordingly, Applicants respectfully request that the rejection of claims 1, 3-6, 8, 9, 16 and 18 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Final Office Action mailed December 13, 2001. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: June 13, 2002



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